



Published in final edited form as:

Chem Commun (Camb). 2017 June 29; 53(53): 7270–7273. doi:10.1039/c7cc00997f.

Exhaustive Suzuki-Miyaura Reactions of Polyhalogenated Heteroarenes with Alkyl Boronic Pinacol Esters

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Abstract

A novel Suzuki-Miyaura protocol is described that enables the exhaustive alkylation of polychlorinated pyridines. This method enables a formal synthesis of normuscopyridine and the rapid assembly of a dumbbell shaped portion of a [2]rotaxane.

The 2-alkylpyridine scaffold is critical to bioactive small molecules, to molecular machines, and within ligands for metal catalyzed transformations (Figure 1).¹ Several powerful approaches have been developed to install alkyl substituents on pre-formed pyridyl cores.² In terms of traditional cross-coupling approaches, 2-pyridyl organometallic reagents have been advanced, but suffer from air instability³ and reaction-specific limitations, including requirements for high catalyst loadings or a narrow range of cross-coupling partners.⁴ A complementary approach involves the direct functionalization of affordable, readily accessible, and chemically stable heteroaryl chlorides by way of a cross-coupling reaction.⁵ The Suzuki-Miyaura reaction relies on commercially available reagents that offer reduced toxicity.^{6,7} Only a few conditions can couple alkyl organoboron reagents with 2-halopyridines.⁸ To complement our disclosed selective and serial Suzuki-Miyaura reactions of polychlorinated pyridines with alkyl pinacol boronic esters (Scheme 1, eq 1, 2),⁹ we now describe an exhaustive Suzuki-Miyaura reaction of haloarenes, including 2-pyridylchlorides (Scheme 1, eq 3).

The challenges in this transformation derive from (1) the ability of the Lewis basic pyridine nitrogen to bind the metal and inhibit further reactivity,¹⁰ and (2) the relatively slow transmetalation of alkyl organoboron species. Slow transmetalation renders decomposition pathways more competitive, including protodehalogenation of aryl halides, protodeborylation¹¹ of the alkyl boronic esters, and β -hydride elimination processes of palladium-alkyl intermediates.

Initially, we chose to interrogate the Suzuki-Miyaura reaction of 2,6-dichloropyridine (**3a**) with heptyl pinacol boronic ester to generate 2,6-dialkylpyridine **5a** (Table 1). The targeted bond-forming reactions do not proceed efficiently using many cutting-edge protocols to

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Electronic Supplementary Information (ESI) available: Full experimental details, copies of NMR spectra (PDF).

couple aryl halides with alkyl boron compounds.¹² We anticipated that this reaction would be promoted by sterically encumbered alkyl phosphine ligands. Such ligands favor formation of mono-coordinated palladium-phosphine complexes, which undergo accelerated oxidative addition,¹³ transmetalation, and reductive elimination processes.¹⁴ Moreover, sterically encumbered ligands can help to mitigate β -hydride elimination following transmetalation of the organoboron species. We found that di(1-adamantyl)-*n*-butylphosphine provided the highest levels of dialkylpyridine **5a** (entries 1–3).

The optimal conditions vary slightly from those disclosed recently to affect the Suzuki-Miyaura reaction of halopyridines with boronic acids (entry 4),¹⁵ but the differences have a dramatic impact on the reaction. Empirical studies with different palladium sources and solvents revealed a beneficial effect derived from the use of a Pd(OAc)₂ pre-catalyst and solvation with 4:1 dioxane:water (entries 4–8). Presumably, water mediates pinacol boronic ester speciation.

Pinacol boronic ester speciation also depends on reaction pH. Reaction conversion increases with increasing basicity (entries 9–12; pK_a of corresponding conjugate acids in water: HF, 3.2; HCO₃[–], 10.2; HPO₄^{2–}, 12.7; HO^tBu, 16.5).¹⁶ Interestingly, the identity of the counter cation resulted in significant differences in conversion to the exhaustively coupled product, presumably due to differences in nucleophilicity (entries 13–14).¹⁷ Lithium alkoxides were the only bases screened that favoured exhaustive coupling over selective coupling (entries 1, 15). Under the optimal conditions, the reaction of 2,6-dichloropyridine with heptyl boronic pinacol ester (2.3 equiv) proceeded in a 4:1 mixture of dioxane:H₂O at 100 °C with LiO^tBu, 1 mol% Pd(OAc)₂ and 3 mol% Ad₂P^{*n*}Bu to afford 2,6-diheptylpyridine (**5a**) in excellent selectivity and 94% isolated yield (entry 1). In general, LiO^tBu is not included as a base during empirical screens of Suzuki-Miyaura reaction conditions.^{12,18} These results suggest that it could be of broad relevance to base-tolerant substrates.

With 2,6-dichloropyridine, exhaustively coupled product **5a** is predominately formed only with an excess of boronic ester **6a**. Conversely, when **6a** is employed as the limiting reagent, selectively coupled **4a** is the major product (entry 16). By contrast, 2,6-dibromopyridine generates nearly exclusively exhaustively coupled **5a** when **6a** is used as the limiting substrate (entry 17). We hypothesize that during the transformation, the palladium catalyst remains ligated to the 2-bromo-6-alkylpyridine intermediate, but can dissociate from 2-chloro-6-alkylpyridine species prior to the second transmetalation event. This differential reactivity could be a consequence of the higher barrier to oxidative addition to aryl chlorides relative to bromides.

Under the optimized conditions, 2,6-dibromo- and 2,6-dichloropyridine react with similar efficiency (entries 1, 18). Consequently, we have chosen to investigate the reaction scope with chloroaromatic electrophiles, which are thought to be more challenging cross-coupling partners, and are often more readily available and less expensive. An array of aryl chlorides couple smoothly with pinacol boronic ester **6b** (Table 2). Mono-, di-, and trichloropyridines are converted to mono-, di-, and trialkylpyridines, respectively (entries 1–3). This protocol tolerates electron-donating substituents on pyridine, which were not effectively transformed under our previously reported selective conditions (entry 4–5),⁹ as well as electron-deficient

aryl chlorides (entry 6). This protocol affects reaction of other 2-chloroheteroaryl compounds, such as isoquinolines (entry 7). In most cases, the starting aryl chloride and the reported product account for the mass balance of the reaction. An exception is 2,6-dichloro-4-trifluoromethyl pyridine, which is known to be unstable at elevated temperatures (entry 8).

These conditions do not productively transform more acidic substrates, such as 6-chloroindole and 6-chloropyridin-2-one, both of which would be expected to be deprotonated under the reaction conditions. Even *p*-chloroacetophenone does not undergo efficient cross-coupling, possibly due to competitive deprotonation (Table 2, entry 10). Relative to HO^tBu, *p*-chloroacetophenone is more acidic in DMSO (pK_a 23.78 vs 32.2), and slightly more basic in water (pK_a 18.1 vs. 16.5.^{16b, 19} Many base-originated limitations can be surmounted through use of a weaker base or by substrate design. For example, substrate redesign permits access to 6-alkylpyridin-2-ones from 2-alkoxy-6-chloropyridines (entry 11). Therefore, this protocol may be used as a launching point for optimization of Suzuki-Miyaura reactions of 2-halopyridines with alkyl boronic esters displaying increased base sensitivity.

Pyridyl chlorides react effectively with alkyl pinacol boronic esters that incorporate distal unsaturation, acetals, or ethers (Table 3, entries 1–8). The clean formation of unsaturated products is notable, as similar selectivity would be difficult to achieve via Heck olefination reactions or Suzuki-Miyaura reactions involving transmetalation of *in situ*-generated organoboranes. Additionally, these unsaturated compounds can be valuable intermediates: the reaction of 2,6-dichloropyridine to form 2,6-dihexenylpyridine constitutes a formal synthesis of the fragrance molecule normuscopyridine, which can be accessed upon ring-closing metathesis and reduction (entry 2).²⁰ As might be expected, these conditions can also be applied to access biaryl compounds (entry 8).

One feature of this exhaustive protocol is that base-sensitive substrates may undergo multiple base-mediated transformations in a single operation. Notably, application of the standard conditions to cross-couple a silyl ether with an activated 2-pyridyl chloride proceeds with desilylation to furnish alcohol **5s** (entry 9). As an alternative, the base labile silyl ether coupling partner is amenable to slightly modified conditions to deliver the intact silylated product (entry 10).

To push the limits of this protocol, we focused on allyl pinacol boronic ester, which is known to be highly reactive and easily protodeborylated (entry 11). While our optimized reaction protocol involving LiO^tBu does not generate the desired product; anhydrous conditions can be applied with a more organic soluble base to promote productive cross-coupling. To the best of our knowledge, this represents the first example of direct Suzuki-Miyaura catalyzed allylation of an aryl chloride, previous reports being limited to the use of more reactive aryl iodides and bromides.

The utility of the disclosed reaction has been demonstrated in the synthesis of a dumbbell shaped molecule for a rotaxane (i.e., **1**). Pyridine **1** has been previously accessed in a longest linear sequence of five steps, or in three steps and 54% yield from common intermediate **9**

via palladium-catalyzed Sonagashira cross-coupling and hydrogenation reactions.^{1d} This new protocol furnishes **1** in two steps and 64% yield from common intermediate **9**. This protocol could assist in the development of new molecular machines, as, in principle, the alkyl boronic ester substrate can be easily modified to access threads of varying length or to generate differentially substituted dumbbell shaped molecules if deployed in sequence with the previously disclosed selective method.⁹

In conclusion, these optimized Suzuki-Miyaura reaction conditions enable the controlled alkylation of series of 2,6-dichloropyridines in presence of unsaturation, etherial linkages, or acetals. The use of bulky $\text{Ad}_2\text{P}^t\text{Bu}$ in combination with LiO^tBu facilitates oxidative addition onto 2-chloro-6-alkylpyridines, thereby forming exhaustively alkylated products. Importantly, these reaction conditions minimize β -hydride elimination processes as well as protodehalogenation of the starting materials. These conditions have been applied to gain efficient access to a known [2]rotaxane component.

This project was funded by the American Chemical Society Petroleum Research Fund Doctoral New Investigator Program (PRF# 54824-DNI1) and by Duke University. J.M.B. was supported by the National Institute of General Medical Sciences (T32GM007105-41). Characterization data were obtained on instrumentation secured by funding from the NSF (CHE-0923097, ESI-MS, George Dubay, the Duke Dept. of Chemistry Instrument Center), or the NSF, the NIH, HHMI, the North Carolina Biotechnology Center and Duke (Duke Magnetic Resonance Spectroscopy Center). Jacob Timmerman and Prof. R. Widenhofer of Duke University are thanked for their insights. Ekaterina Khlystova and Brendan Sweeney are thanked for their contributions to initial investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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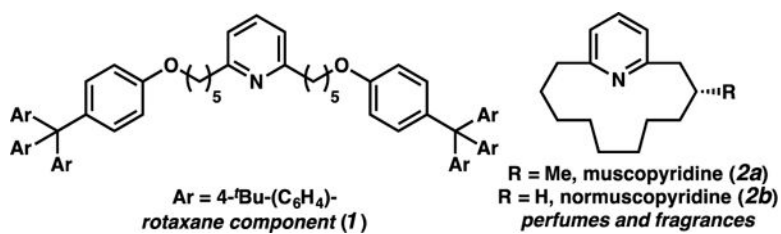
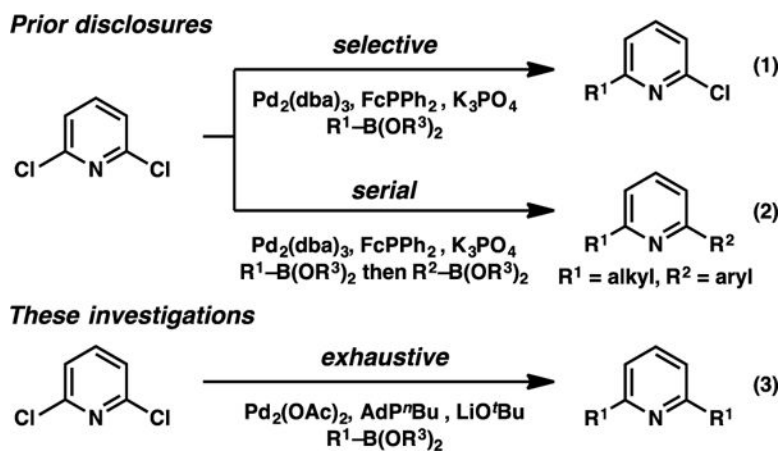
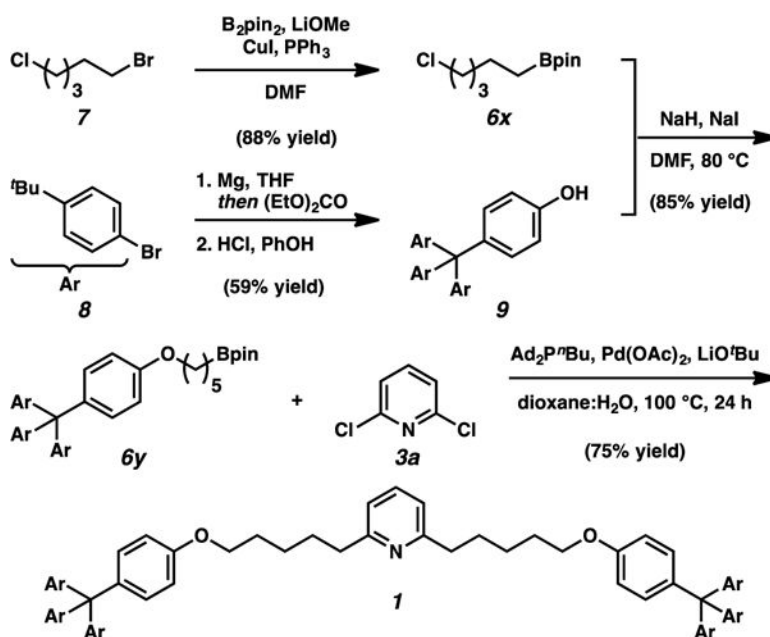


Figure 1.
Utility of the 2-alkylpyridines^{1b,d}



Scheme 1.
Prior disclosures and these investigations



Scheme 2.

Application to the synthesis of a dumbbell shaped molecule for a rotaxane

Table 1

Influence of base, ligand, and palladium source on reaction outcome

entry	Pd source	X	equiv 6a	solvent	base	4a (%) ^a 5a (%) ^a
1	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	LiO ^t Bu	nd ^b 94 ^c
2 ^d	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	LiO ^t Bu	25% 5%
3 ^e	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	LiO ^t Bu	52% 6%
4	Pd ₂ (dba) ₃	Cl	2.3	PhMe	K ₃ PO ₄	5 nd ^b
5	Pd ₂ (dba) ₃	Cl	2.3	dioxane/H ₂ O	LiO ^t Bu	5 90
6	Pd(OAc) ₂	Cl	2.3	dioxane	LiO ^t Bu	<5 nd ^b
7	Pd(OAc) ₂	Cl	2.3	PhMe/H ₂ O	LiO ^t Bu	40 <5
8	Pd(OAc) ₂	Cl	2.3	PhMe	LiO ^t Bu	<5 nd ^b
9	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	CsF	29 <5
10	Pd(OAc) ₂	Cl	2.3	dioxane	CsF	5 nd ^b
11	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	Cs ₂ CO ₃	72 7
12	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	K ₃ PO ₄	73 13
13	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	NaO ^t Bu	68 8
14	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	KO ^t Bu	39 31
15	Pd(OAc) ₂	Cl	2.3	dioxane/H ₂ O	LiOMe	33 66
16	Pd(OAc) ₂	Cl	1.0	dioxane/H ₂ O	LiO ^t Bu	56 20
17	Pd(OAc) ₂	Br	1.0	dioxane/H ₂ O	LiO ^t Bu	nd ^b 48
18	Pd(OAc) ₂	Br	2.3	dioxane/H ₂ O	LiO ^t Bu	nd ^b 94

^aDetermined by ¹H NMR.^bnd = Not detected.

Tricyclohexylphosphine used in place of $\text{Ad}_2\text{P}^t\text{Bu}$.

d FePPh_2 used in place of $\text{Ad}_2\text{P}^t\text{Bu}$.

c Isolated yield.

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
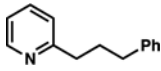
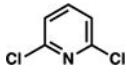
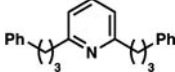
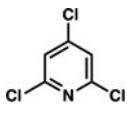
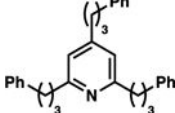
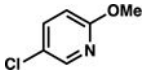
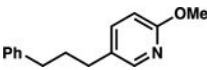
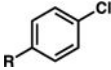
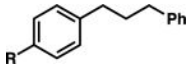
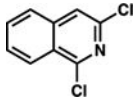
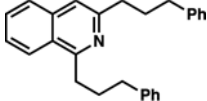
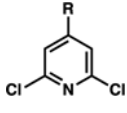
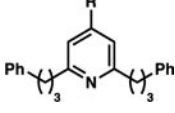
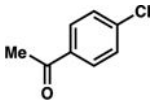
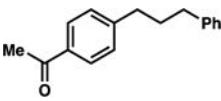
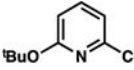
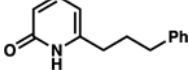
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Table 2

A general procedure for Suzuki-Miyaura reactions of aryl chlorides

$\text{ArCl} + \text{pinB-CH}_2\text{CH}_2\text{CH}_2\text{Ph} \xrightarrow[\text{dioxane/H}_2\text{O (4:1), 100 }^\circ\text{C, 24 h}]{\text{Ad}_2\text{P}^n\text{Bu, Pd(OAc)}_2, \text{LiO}^t\text{Bu}}$ $\text{Ar-CH}_2\text{CH}_2\text{CH}_2\text{Ph}$			
entry ^a	ArCl	product	yield (%) ^b
1 ^c			5b, 81
2			5c, 95
3 ^d			5d, 82
4 ^{c,e}			5e, 98
5 ^{e,f} 6 ^{e,f}			5f, 90 5g, 90
7 ^g			5h, 84
8 9			5i, 52 5j, 96
10 ^{c,d}			5k, 18
11 ^{e,h}			5l, 99

^a General reaction conditions: 1.0 equiv aryl chloride, 0.105 M dioxane/H₂O (4:1), 2.3 equiv R²Bpin, 1 mol % Pd(OAc)₂, 3 mol % Ad₂PⁿBu, 6.0 equiv LiO^tBu, 24 h, 100 °C.

^b Isolated yield.

^c 2 mol % Pd(OAc)₂, 6 mol % AdPⁿBu.

^d 3.5 equiv R²Bpin, 9.0 equiv LiO^tBu.

^e 1.5 equiv R²Bpin, 3.0 equiv LiO^tBu.

^f 20 h.

^g 16 h.

^h Isolated after reaction with trifluoroacetic acid.

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Table 3

Functional group tolerance in disclosed Suzuki-Miyaura reactions

entry ^a	R ¹	organoboron	product
1	Cl	pinB-CH=CH ₂	5m, 90
2	Cl	pinB-CH=CH ₂	5n, 85
3 ^c	Cl	pinB-CH=CH(R ³)	5o, 44
4 ^d	Cl	pinB-CH=CH(R ⁴)	5p, 45
5 ^{c,e,f}	tBuO	pinB-CH=CH(R ³)	5q, 85
6 ^{d,e,f}	tBuO	pinB-CH=CH(R ⁴)	5r, 84
7 ^f	tBuO	pinB-CH=CH(R ³)	5s, 90
8 ^g	tBuO	(HO) ₂ B-Ph	5t, 99
9 ^f	tBuO	pinB-CH=CH(OTBS)	5u, 84
10 ^g	tBuO	pinB-CH=CH(OTBS)	5v, 89
11 ^{e,i}	tBuO	pinB-CH=CH ₂	5w, 47

^a General reaction conditions: 1.0 equiv aryl chloride, 0.105 M dioxane/H₂O (4:1), 2.3 equiv R²-Bpin, 1 mol % Pd(OAc)₂, 3 mol % Ad₂P(tBu)₂, 6.0 equiv LiOtBu, 24 h, 100 °C.^b Isolated yield.

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^c Pinacol boronic ester and product have isomeric ratios of >19:1 *E:Z*.

^d Pinacol boronic ester and product have isomeric ratios of >19:1 *Z:E*.

^e Isolated after reaction with trifluoroacetic acid.

^f 1.5 equiv R²Bpin, 3.0 equiv LiO^tBu.

^g 1.5 equiv R¹Bpin, 3.0 equiv K₃PO₄, no LiO^tBu.

^h 1.5 equiv PhB(OH)₂, no R²Bpin, 3.0 equiv LiO^tBu, 18 h.

ⁱ 4.0 equiv CsF, no LiO^tBu.